1 H), 2.02 (ddd, 1 H, J = 13.0, 3.6, 2.7 Hz), 2.30 (dd, 1 H, J = 17.4, 12.0 Hz), 2.40 (dd, 1 H, J = 17.4, 9.6 Hz), 2.67 (m, 1 H), 4.10 (d, 1 H, J = 8.1 Hz).

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A Versatile Synthesis of 1,1-Dioxo 7-Substituted Cephems: Preparation of the Human Leukocyte Elastase (HLE) Inhibitor 1,1-Dioxo-*trans*-7-methoxycephalosporanic Acid *tert*-Butyl Ester

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A four-step synthesis of the human leukocyte elastase (HLE) inhibitor 1,1-dioxo-*trans*-7-methoxycephalosporanic acid *tert*-butyl ester in 44% isolated yield from 7-aminocephalosporanic acid (7-ACA) is described. A variety of 7-substituents have been introduced via metal-catalyzed diazo insertion reactions, and the use of a flow reactor for chemodiscriminate control of particularly rapid reactions is presented. A chemoselective oxidation of 7-ACA *tert*-butyl ester to the corresponding 1,1-dioxide without formal N-protection is introduced.

Introduction

Neutral proteolytic enzymes, specifically human leukocyte elastase (HLE) released from human polymorphonuclear (PMN) leukocytes, have been implicated in the pathogenesis of adult respiratory distress syndrome (ARDS), emphysema, and rheumatoid arthritis.[1] Inhibition of HLE, therefore, may attenuate the onset of such diseases. Several laboratories, including our own, have instituted a search for compounds which show promise as in vivo inhibitors of HLE. At least four general classes of compounds have been identified which exhibit in vitro inhibition of HLE models.[2] These classes include 2-furoylsaccharin-, isotoic anhydride-, cephalosporin-,[3-5] and peptide-based compounds. In evaluating modified cephalosporin-based HLE inhibitors, we were presented with the opportunity to devise an adaptable and high-yielding general synthesis for the preparation of 1,1-dioxo 7-substituted cephems from the relatively inexpensive starting material 7-aminocephalosporanic acid (7-ACA). Our initial target was 1,1-dioxo-*trans*-7-methoxycephalosporanic acid *tert*-butyl ester (8), which has been established by Doherty et al.[6] as a compound showing strong in vitro inhibition of HLE.

With 7-ACA as starting material, it was obvious that any synthesis of 8 must effect two key chemical transformations, i.e. conversion of the *cis*-7-amino group to the *trans*-7-methoxy group and oxidation of the 1-sulfide to the corresponding 1-sulfone. The original procedure of Doherty accomplished these transformations via diazotization of 7-ACA-O-*t*-Bu followed by rhodium-catalyzed insertion into methanol and subsequent oxidation of the 7-methoxy sulfide with *m*-chloroperbenzoic acid (*m*-CPBA).[7] Due to the inherent problems associated with carbene (carbenoid) interaction with sulfide,[8] the insertion reaction on a relatively unstable diazo compound gave low yields of a key intermediate. During our investigation we discovered that if we transposed the reaction sequence so that S-oxidation occurred first, subsequent diazotization/insertion on the resulting sulfone improved dramatically to >90%. Furthermore, the intermediate diazo sulfone proved to be particularly useful for the preparation of other 7-substituted sulfone cephems which were either heretofore unknown or obtained only with great difficulty.

Our approach to an adaptable synthesis which would serve to supply the required 8 and yet be easily modified to supply other 7-substituted cephems from a common intermediate is presented below.

Discussion

1. 7-Aminocephalosporanic Acid *tert*-Butyl Ester (2). Our preparation of 7-ACA *tert*-butyl ester was based on the procedure described by Stedman[9] (52%). Existing reports in the literature for the preparation of this compound were sketchy, and further optimization of this reaction proved quite instructive. Superficially, this reaction can be viewed as a simple equilibrium between 7-ACA and and 7-ACA-O-*t*-Bu mediated by isobutylene. However, the reaction is actually comprised of a complex series of equilibria involving protonated 7-ACA and protonated isobutylene. The role of the acid catalyst is manifold. The acid catalyst must: (1) protonate the amino group of 7-

(1) Bonney, R. J.; Smith, R. J. *Advances in Inflammation Research*; Otterness, I., et al., Eds.; Raven Press: New York, 1986; Vol. 11.
(2) *Chem. Eng. News.* **1987**, *65*(17), 37-38. (Preliminary report on the ACS national meeting in Denver, CO, April 6, 1987).
(3) Doherty, J. B.; Ashe, B. M.; Bonney, R. J.; Finke, P. E.; Thompson, K. R.; Shah, S. K.; Zimmerman, M. U.S. Patent 4,547,371, 1985.
(4) Doherty, J. B.; Ashe, B. M.; Finke, P. E.; Firestone, R. A.; Shah, S. K.; Zimmerman, M. U.S. Patent 4,623,645, 1986.
(5) Doherty, J. B.; Finke, P. E.; Firestone, R. A.; Shah, S. K.; Thompson, K. R. U.S. Patent 4,637,999, 1987.
(6) Doherty, J. B.; Ashe, B. M.; Argenbright, L. W.; Barker, P. L.; Bonney, R. J.; Chandler, G. O.; Dahlgren, M. E.; Dorn, C. P., Jr.; Finke, P. E.; Firestone, R. A.; Fletcher, D.; Hagmann, W. K.; Mumford, R.; O'Grady, L.; Maycock, A. L.; Pisano, J. M.; Shah, S. K.; Thompson, K. R.; Zimmerman, M. *Nature* **1986**, *322*, 192-194.
(7) Doherty, J. B.; Finke, P. E.; Shah, S. K., manuscript in preparation.
(8) John, D. I. *Spec. Publ. R. Soc. of Chem.* **1985**, *52*, 193-208.
(9) Stedman, R. J. *J. Med. Chem.* **1966**, *9*, 444.

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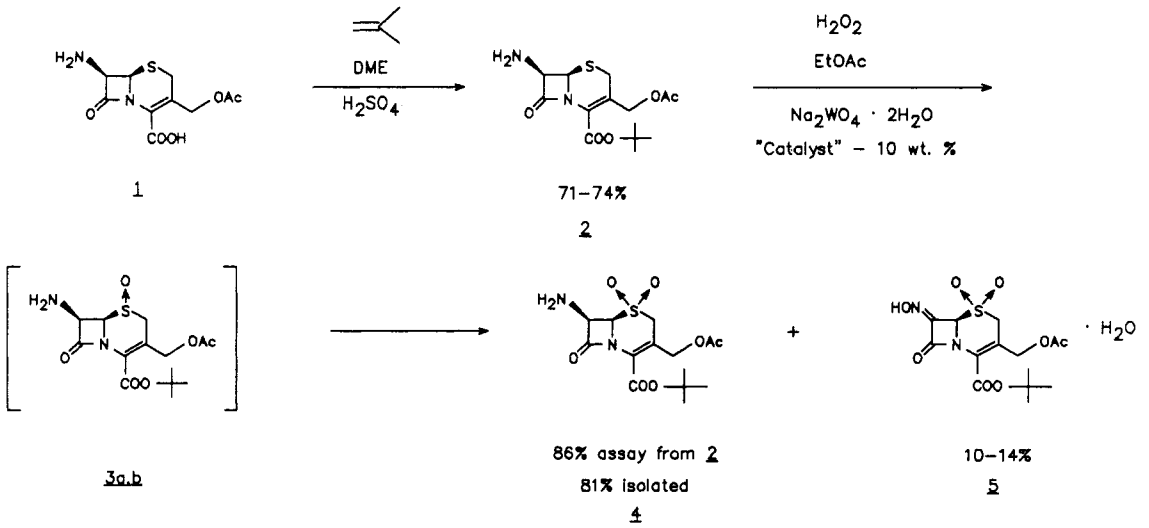
Scheme I



ACA to protect it from electrophilic attack; (2) solubilize the 7-ACA in the solvent medium as an acid/base salt; and (3) be sufficiently strong to protonate isobutylene and drive the esterification reaction without inducing excessive polyisobutylene formation. Choice of solvent was critical. Due to safety concerns, *p*-dioxane, the classical solvent of choice for the acid-catalyzed esterification of amino acids with isobutylene, was replaced with 1,2-dimethoxyethane (DME). Laboratory experiments using DME, however, have consistently afforded 5–7% lower yields and have taken longer to reach equilibrium.

The charge ratio of 7-ACA:sulfuric acid:isobutylene was also critical; a ratio of 1:>4.8:>22 was necessary to consistently drive the equilibrium above an 80:20 ratio of 7-ACA *tert*-butyl ester:7-ACA. Larger excesses could drive the reaction further, but we felt that a point of diminishing returns had been reached. A controlled quench of the reaction mixture into cold aqueous sodium bicarbonate solution, extraction into isopropyl acetate, and crystallization from isopropyl acetate/hexanes afforded a 71–74% isolated yield of 7-ACA *tert*-butyl ester.

Evaluation of alternative solubilizing acids such as benzenesulfonic acid and *p*-toluenesulfonic acid in *p*-dioxane and alternative aprotic solvents gave only minor yield gains. These gains weighed unfavorably against the extra step and expense of preparing these acids in the required anhydrous form from their commercially available hydrates.

Multistep procedures requiring N-protectin of 7-ACA and/or separate activation of the carboxylic acid group were not examined.

2. 7-Amino-1,1-dioxocephalosporanic Acid *tert*-Butyl Ester (4). A low-yielding four-step preparation of **4** via *m*-CPBA oxidation of BOC-7-ACA-*O*-*t*-Bu and selective deprotection has previously been reported by Durckheimer.[10] The direct oxidation of 7-ACA *tert*-butyl ester to the corresponding sulfone was, therefore, quite attractive but posed some unique problems due to the potential for N-oxidation of the 7-amino group. As in step one above, we believed that protection from N-oxidation might come via protonation of the amine prior to oxidation.[11] Attempts using various combinations of acetic, formic, and sulfuric acids in conjunction with peracetic acid, *m*-chloroperbenzoic acid, and hydrogen peroxide were unsuccessful. We were partially successful, however, via formation of the *p*-toluenesulfonate salt of 7-ACA *tert*-butyl ester. Subsequent oxidation with *m*-chloroperbenzoic acid afforded nearly 80% of the desired sulfone. However, direct oxidation without N-protection was ultimately effected catalytically with sodium tungstate[12] and 30% aqeuous hydrogen peroxide in a suitable solvent (the oxidizing species being pertungstic acid). The solvent of choice, ethyl acetate, was key to obtaining a >80% yield of sulfone. Methylene chloride, acetic acid, and methanol afforded much lower yields. The secondary oxidation of sulfoxide to sulfone failed to complete without byproduct formation. The substitution of vanadyl acetylacetonate under identical conditions gave similarly low yields. Even in ethyl acetate the hydrogen peroxide/sodium tungstate reaction was not without drawback. Some N-oxidation indeed occurred to form 10–14% of a nearly insoluble and crystalline byproduct identified as the 7-hydroxyimino sulfone derivative **5** of 7-ACA *tert*-butyl ester. This byproduct did not form as a result of overreaction of sulfone **4**, but was shown to arise from either primary N-oxidation of starting material and/or subsequent N-oxidation of sulfoxide intermediates.

The oxime sulfone **5** was determined to be potentially detonable in dry solid form. Ethyl acetate–wet oxime sulfone, however, could be handled safely. A procedure was devised to avoid its isolation by in situ solubilization and decomposition with aqueous sodium carbonate.

The above oxidation was based on a report by Schultz et al.[13] for the oxidation of sulfides to sulfones. Prior to this report the primary use for sodium tungstate/hydrogen peroxide was for the oxidation of primary amines to the corresponding aldoximes.[14] To our knowledge no one has placed these oxidations in relative perspective. Thus, as far as 7-aminocephalosporins are concerned, our observations suggest that under our conditions the two-step oxidation of sulfide to sulfoxide to sulfone occurs approximately 6 times faster than the two-step oxidation of a

(10) Durckheimer, W.; Klesel, N.; Limbert, M.; Schrinner, E.; Seeger, K.; Seliger, H. *Spec. Publ. R. Soc. of Chem.* **1981**, *38*, 46–56.

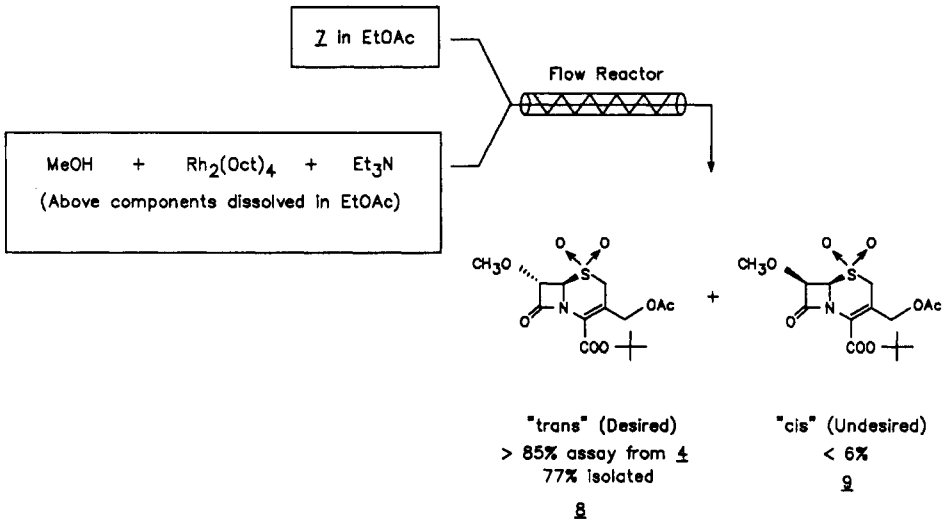
(11) The concept of employing a proton for amine protection has been applied to the S,S-dioxidation of 6-APA with potassium permanganate. See: Bos, J. J.; Cuperus, R.; Wielinga, R. U.S. Pat. 4,695,628. The feasibility of extending this procedure to 7-ACA was not explored.

(12) Connon, N. W. *Eastman Organic Chemical Bulletin* **1972**, *44*, 1–4.

(13) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

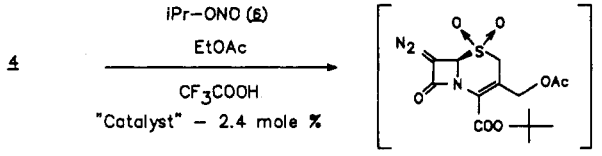
(14) (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 475. (b) Kahr, K.; Berther, C. *Chem. Ber.* **1960**, *13*, 132. (c) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233.

Scheme II



primary amine to aldoxime (oxime) via hydroxylamine.

3. 1,1-Dioxo-*trans*-7-methoxycephalosporanic Acid *tert*-Butyl Ester (8). During the course of evaluating alternative synthetic routes to 8 we discovered that diazotization of the sulfone analogue of 7-ACA *tert*-butyl ester (4) afforded the corresponding diazo sulfone 7, which was orders-of-magnitude more stable in solution[15] and much less dependent on the purity of starting material than the corresponding diazosulfide reported by Wiering and Wynberg.[16] Furthermore, 7 could be generated under homogeneous reaction conditions in near quantitative yield from 4 with standard diazotizing reagents such as isoamyl nitrite (acid catalyzed). A switch to isopropyl nitrite[17] was made to facilitate workup since the reaction byproduct, isopropyl alcohol, could be readily removed from the reaction mixture by vacuum replacement concentration.



> 95%
7

Whereas rhodium-catalyzed insertion reactions of Wynberg's diazo sulfide with methanol afforded poor yields of trans-insertion adduct (averaging 20–25%), the same insertion reaction using our diazo sulfone 7 showed a dramatic improvement. Under optimum conditions we have consistently obtained a two-step assay yield (diazotization and insertion) of >85% of desired 1,1-dioxo-*trans*-7-methoxycephalosporanic acid *tert*-butyl ester (8) at trans/cis isomer ratios >17:1.

The intermediate carbene (carbenoid) generated from the diazo sulfone was much more chemodiscriminate than that derived from the diazo sulfide. Two major products identified as *trans*- and *cis*-7-methoxy 8 and 9 were formed in high yield.[18] Typical first-choice conditions for the desired insertion reaction (20 wt % rhodium catalyst[19] in MeOH and CH_2Cl_2) gave 40–55% yield of a 3:1 mixture trans/cis isomers. Initial experiments performed at HPLC concentrations (0.1 mg/mL) to avoid bimolecular reactions (dimerization) showed that more polar solvents could raise the yield dramatically. In methanol, a nearly quantitative, yet nonstereoselective, insertion (1:1 trans:cis) was obtained. The obvious conclusions were to eliminate the nonpolar cosolvent and to minimize the amount of reagent methanol so as to increase stereoselectivity. Among the more polar cosolvents tried, cyclic ethers such as THF and dioxane gave the highest yields at a methanol charge of approximately 5 vol %. Also, a large excess of catalyst was not necessary, and in fact, it was detrimental to optimization of the trans/cis ratio. While a fast reaction rate ensured a higher insertion yield, slowing down the rate of reaction with a reduced methanol and catalyst charge increased stereoselectivity. Temperature was also found to influence yield and ratio. These conflicting rate requirements were optimized by empirical adjustment of reaction conditions to maintain a 10–30 s half-life relative to diazo reagent. Longer reactions did not complete and afforded lower yields. As scale increased and instantaneous mixing of reactants became nearly impossible, a continuous flow reactor was devised for our preparative efforts (Scheme II). This device allowed for the exact and instant mixing of reagents, critical maintainance of concentration and stoichiometry, an increase in the reagent concentrations to 100 mg/mL (0.27 M), and controlled evolution of nitrogen gas byproduct. Another change necessitated by large-scale preparation was the replacement of ethereal solvents with ethyl acetate, which performed nearly as well when its basicity was increased with a small amount of triethylamine. The present procedure utilizes a Kenics static mixer flow tube. A residence time of 1–3 min (6 half-lives) was necessary for complete reaction. Shorter residence times resulting in dilution of the reaction mixture in the receiving vessel gave lower yields and poor trans:cis ratios. Two cold (0 °C) ethyl acetate solutions, one containing rhodium octanoate,[19] methanol, and triethylamine,

(15) We note that this diazo compound 7 was determined by our Occupational Hazards Evaluation Laboratory (OHEL) to be shock sensitive and potentially detonable when crystalline. It was also determined, however, to be safely handleable in solutions of up to 10 wt % in methylene chloride or ethyl acetate.

(16) Wiering, J. S.; Wynberg, H. *J. Org. Chem.* **1976**, *41*, 1574–1578.

(17) Levin, N.; Hartung, W. H. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 191–193.

(18) We believe this to be the first example of a *cis*-alkoxy insertion product arising from the metal-catalyzed reaction of a diazocephalosporin with an alcohol.

(19) A homogeneous catalyst, rhodium octanoate dimer, purchased from Johnson-Matthey, Inc., Chemicals Division, Winslow, NJ 08095, and necessary for flow reactor use, replaced the more traditional and less soluble rhodium acetate dimer. Stationary-bed catalysts were not examined.

and the other freshly prepared unisolated diazocephalosporin 7, were pumped (metered) together at equal rates so that complete reaction was obtained in the flow reactor and/or appendant tube before discharge into the receiving vessel.

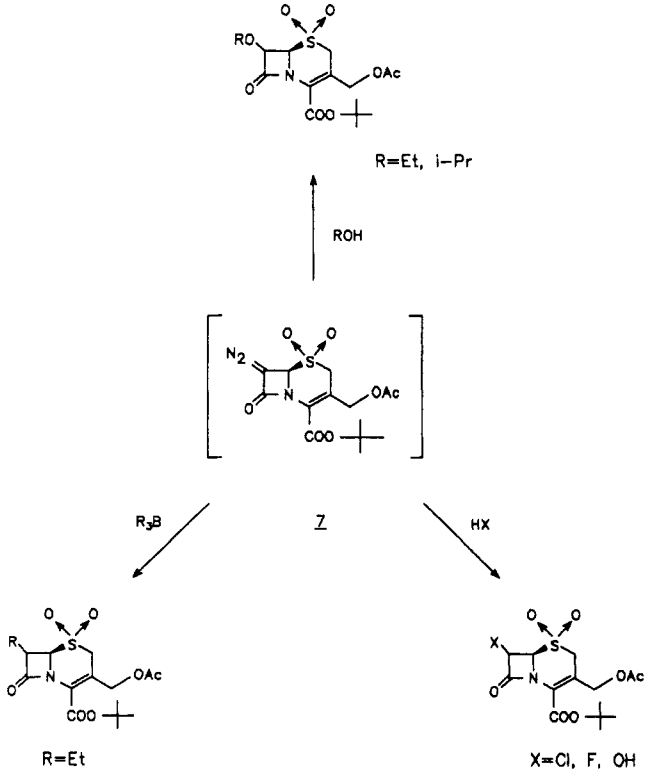
Scope of Insertion Reaction

Diazocephalosporin 7 was found to undergo some of the typical transformations associated with stabilized diazo compounds.

On reaction with HCl the predominantly *trans*-7-chloro compound was formed in high yield. As with the insertion reactions described above, this reaction, too, afforded small amounts of 7-cis adduct, which was readily isolated and identifiable by ^{1}H NMR spectroscopy on the basis of a characteristic vicinal coupling (J_{cis} = 5.0–6.0 Hz) in the β-lactam moiety. Even hydrogen fluoride (via HF/pyridine complex) gave the corresponding *cis*- and *trans*-7-fluoro derivatives, albeit in poor yield.

Rhodium-catalyzed insertion reactions worked well on the lower aliphatic alcohols (R = Me, Et, *i*-Pr) to afford predominantly *trans*-alkoxy adducts. Other than the specific case discussed above for methanol, no attempts were made to optimize the reactions with ethanol or 2-propanol, either for yield or for isomer ratio. In each case, however, the cis-insertion products were readily isolable by silica gel chromatography and identifiable by their characteristic ^{1}H NMR spectra. In all cases, a small amount of the *trans*-7-hydroxy adduct was observed by HPLC (identified after isolation and characterization from the reaction of 7 with HF in pyridine) and presumed to arise via insertion into water.

Reaction of 7 with triethylborane in similar fashion to the procedure described by Weiring and Wynberg[16] afforded the expected 7-ethyl derivatives in high chemical yield at an approximate 1:1 cis:trans ratio.



Conclusion

The procedures presented above provide easy entry into a variety of 7-substituted sulfone cephems in generally high yields. In particular, use of a flow reactor has safely achieved control of the rapid intermolecular diazo insertion reaction of 7 with methanol while maintaining yield and stereospecificity. The cephems prepared can be further functionalized to provide a vast array of potentially therapeutic agents.

Experimental Section

NMR spectra were recorded on a Varian XL-300 or a Brucker AM-250 spectrometer in $CDCl_3$ or DMSO-d_6 referenced to tetramethylsilane (TMS) at 0.0 ppm. All coupling constants are presented in hertz (Hz). FTIR spectra were obtained on a Nicolet 7199 spectrophotometer. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus. UV spectra were obtained on a Cary 210 spectrophotometer. Specific rotations were recorded on a Perkin-Elmer 241 polarimeter. All reagent charges and yields were corrected for purity. The term "assay" implies an HPLC wt % analysis against an external standard. The static flow mixer/reactor, part no. 1/4-40-174-0 was purchased from Chemineer/Kenics Div., Kenics Park, N. Andover, MA 01845.

***tert*-Butyl 7-Aminocephalosporanate (2).** To a 12-L jacketed round-bottomed flask fitted with a high-torque agitator, high-efficiency reflux condenser, adjustable diptube inlet, and overhead nitrogen bubbler was charged a slurry of 7-ACA (1, 436 g, 1.6 mol) in 1,2-dimethoxyethane (4.0 L, KF ≤0.05 mg/mL). The slurry was cooled to 5 °C and was maintained at ≤15 °C as concentrated sulfuric acid (400 mL, 7.5 mol) was slowly added. The mixture, now homogeneous, was further cooled to 4–6 °C, and liquified isobutylene (3.0 L, 32 mol) was slowly added subsurface over approximately 2 h via the diptube. [**CAUTION!** The temperature of the reaction was found to be critical and must be maintained near 5 °C. At temperatures below 5 °C the reaction was sluggish. Above 10 °C the isobutylene readily boiled/evaporated away. The mixture generally clouded on addition of isobutylene and remained biphasic for 2–6 h.] The reaction was stirred at 5 °C for 3 days and was checked periodically by HPLC for the product–starting material ratio.

The reaction was deemed over when the normalized ratio of product–starting material was 85:15 area % by HPLC (see conditions below), or no further increase in product–starting material ratio was observed on continued age. Additional time was sometimes required to reach the 85:15 equilibrium. Laboratory runs generally required 3 days.

When the reaction was deemed complete, the batch was slowly quenched into a well-stirred mixture of saturated aqueous sodium bicarbonate (14.0 L, 16.7 mmol) and isopropyl acetate (4.0 L) at 5 °C. Vigorous evolution of CO_2 occurred. The pH of the aqueous layer was checked during the quench to assure that it was basic (pH >7.0). (Additional sodium bicarbonate was added to the mixture if necessary.) The biphasic mixture was stirred for 10 min, after which the layers were allowed to separate. The lower aqueous layer was removed and reextracted with isopropyl acetate (2 × 4.0 L). The combined isopropyl acetate extracts were dried over sodium sulfate (500 g), filtered, and assayed for product by HPLC against an external standard (see HPLC conditions below). The yield of 7-ACA-O-*t*-Bu was 405–421 g (77–80%).

The product solution was then concentrated under vacuum at ≤25 °C to 1.1 L. Crystallization of the product ensued near the end of the concentration. At this point hexanes (4.1 L) was slowly added to the stirred product mixture. The batch was aged for 2 h, cooled to 0–5 °C, and aged for an additional 2–4 h. The product was filtered, washed with hexanes (1 L), sucked well, and dried in vacuo at 40 °C to constant weight. The isolated yield of 7-ACA-O-*t*-Bu (2) was 373–389 g (71–74% corr. for purity by HPLC wt %). HPLC conditions: column, C-8 Altex Ultrasphere 5 μm (4.1 mm × 25 cm); eluant, 60:40 A:B isocratic at 2.0 mL/min, A=H_2O (0.1% H_3PO_4 v/v), B=CH_3CN; temperature, 50 °C; detector, UV at 260 nm; t_R 7-ACA (1) 2.31 min, t_R 7-ACA-O-*t*-Bu (2) 7.4 min. ^{1}H NMR ($CDCl_3$): δ 5.03 (d, 1 H, J = 13.5), 4.94 (d, 1 H, J = 5.2), 4.79 (d, 1 H, J = 13.5), 4.76 (d, 1 H, J = 5.2), 3.55 (d, 1 H, J = 18.3), 3.35 (d, 1 H, J = 18.3), 2.09 (s, 3 H), 1.76 (br s, NH_2), 1.54 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 170.7 (s), 168.3 (s), 160.7 (s), 127.8 (s), 122.5 (s), 83.7 (s), 63.6 (s), 63.3 (s), 58.7

(s), 27.8 (s), 26.1 (s), 20.8 (s). Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.18; H, 6.09; N, 8.53; S, 9.77. Found: C, 51.11; H, 6.25; N, 8.74; S, 9.77.

***tert*-Butyl 7-Amino-1,1-dioxocephalosporanate (4).** In a 4-L three-necked round-bottomed flask equipped with a mechanical agitator and provision for external cooling/heating was dissolved *tert*-butyl 7-aminocephalosporanate (**2**, 100 assay g, 0.305 mol) in ethyl acetate (2.0 L) at 25 °C. The solution was stirred rapidly as solid sodium tungstate dihydrate (10.0 g, 0.0305 mol) and 30% hydrogen peroxide (125 mL, 1.22 mol) were added. The temperature of this now biphasic mixture was maintained at 20–25 °C with cooling for 2 h.

The reaction temperature immediately began to rise on addition of the 30% peroxide, and thus a cooling bath was used from the start to keep the temperature at ≤25 °C. The reaction mixture took on a yellow cast due to the formation of the oxidizing species sodium pertungstate.

After 2 h, an additional charge of 30% hydrogen peroxide (25 mL, 0.25 mol) was made, and the batch was aged until complete, as judged by HPLC (10–18 h) (see conditions below). An additional periodic charge of 30% hydrogen peroxide (25 mL, 0.25 mol) was made if the reaction failed to complete within 18 h. Laboratory reactions were typically allowed to run overnight. The formation of sulfone product proceeded via two diastereomeric sulfoxide intermediates which were differentiable by HPLC. Two minor impurities were also observed by HPLC, one the oxime sulfone **5** (t_R 8.0 min) and an unknown (t_R 6.7 min). The oxime sulfone **5** was only sparingly soluble in the reaction medium, and the bulk of it crystallized out. Filtration afforded 5–10% of a white crystalline solid, mp 183 °C dec, which was identified as 1,1-dioxo-7-(hydroxyimino)cephalosporanate monohydrate (**5**) on the basis of its spectral characteristics. ^{1}H NMR (DMSO-d_6): δ 5.77 (s, 1 H), 5.16 (d, 1 H, J = 13.0), 4.63 (d, 1 H, J = 13.0), 4.02 (d, 1 H, J = 18.6), 3.70 (d, 1 H, J = 18.6), 3.47 (s, 1 H, OH), 2.10 (s, 3 H), 1.60 (s, 9 H). ^{13}C NMR (DMSO-d_6): δ 170.3 (s), 159.5 (s), 156.7 (s), 148.5 (s), 127.2 (s), 116.6 (s), 83.6 (s), 69.2 (s), 62.9 (s), 45.9 (s), 27.5 (s), 20.7 (s). Anal. Calcd for $C_{14}H_{18}N_2O_8S$: C, 42.86; H, 4.85; N, 7.48; S, 8.56. Found: C, 43.28; H, 5.27; N, 7.19; S, 8.27. [**CAUTION**! Our Occupational Hazards Evaluation Laboratory has determined dry oxime byproduct **5** to be shock sensitive and possibly detonable. Ethyl acetate–wet oxime, however, was not shock sensitive and could be dealt with by in situ reaction (decomposition) with aqueous sodium carbonate.]

Thus, as an alternative the reaction was worked up in the following manner. After the reaction was deemed complete the mixture was diluted with ethyl acetate (3 L) and cooled to 10 °C. The reaction mixture was stirred well while a solution of sodium sulfite (100 g, 0.8 mol) in water (2.0 L) was added slowly to decompose any remaining hydrogen peroxide. [**NOTE**! Dilution of the reaction mixture to >40 mL ethyl acetate/g sulfone was necessary to prevent premature crystallization. Redissolving crystallized sulfone was very difficult.] After 10 min a test for residual peroxide was performed (starch iodide), and, if necessary, additional sodium sulfite was added. The biphasic mixture was further cooled to 5 °C, and a cold (5 °C) solution of aqueous sodium carbonate (2.0 L, 0.153 M, 0.306 mol) was slowly added to decompose oxime byproduct. The mixture was stirred for 10 min. Stirring was discontinued, and the layers were allowed to separate (15 min). The lower aqueous layer was removed and discarded. The upper ethyl acetate product layer was then washed with saturated sodium chloride (1 L). The upper ethyl acetate layer was dried over sodium sulfate (100 g), filtered, and the cake washed with ethyl acetate (1.0 L). The combined filtrate and wash was assayed by HPLC to contain 94.4 g of amino sulfone **4** (86.0%). The batch was concentrated under vacuum at ≤30 °C to 900 mL. Crystallization occurred during concentration. Hexanes (1.6 L) was slowly added to the stirred product slurry, and the batch was aged with stirring for 2 h at 20–25 °C and then for 2 h at 0–5 °C. The product was filtered and rinsed with hexanes (500 mL), sucked well, and dried in vacuo at 30 °C to constant weight. The yield of **4** was 90.7 g (81.0% corr. for 98.0 wt % assay by HPLC). HPLC conditions: column, C-8 Altex Ultrasphere 5 μm (4.1 mm × 25 cm); eluant, 70:30 A:B isocratic at 2.0 mL/min, A=H_2O (0.1% H_3PO_4 v/v), B=CH_3CN; temperature 50 °C; detector UV at 260 nm; t_R 7-ACA-O-*t*-Bu (**2**), 11.2 min; t_R sulfone **4**, 8.7 min; t_R sulfoxides **3a,b**, 6.0 min; t_R oxime **5**, 8.0 min; t_R unknown, 6.7 min. ^{1}H NMR ($CDCl_3$): δ 5.12 (d, 1 H, J = 14.0), 4.91 (d, 1 H, J = 4.9), 4.76 (d, 1 H, J = 4.9), 4.74 (d, 1 H, J = 14.0), 3.94 (d, 1 H, J = 18.6), 3.66 (d, 1 H, J = 18.6), 2.33 (br s, 2 H, NH_2), 2.09 (s, 3 H), 1.54 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 170.4 (s), 167.4 (s), 159.5 (s), 126.4 (s), 122.1 (s), 84.7 (s), 68.4 (s), 66.2 (s), 62.2 (s), 51.9 (s), 27.8 (s), 20.7 (s). FTIR (cm^{-1}) 3408, 1771, 1740, 1713, 1638, 1316, 1232. Anal. Calcd for $C_{14}H_{20}N_2O_7S$: C, 46.66; H, 5.59; N, 7.77; S, 8.90. Found: C, 46.83; H, 5.66; N, 7.94; S, 8.66.

Isopropyl Nitrite (6). The following procedure was based on a report by Levin and Hartung.[17] [**NOTE**! All the following operations were performed under a nitrogen atmosphere. Strict adherence to the recommended temperatures was important to prevent product loss due to evaporation. Isopropyl nitrite boils at 39–40 °C.]

A biphasic mixture consisting of methylene chloride (500 mL), deionized water (3.1 L), and sodium nitrite (681 g, 9.9 mol) was prepared in a 5-L three-neck round-bottomed flask fitted with an overhead nitrogen bubbler and cooled to 0 °C. The mixture was stirred well as a solution of isopropyl alcohol (690 mL, 8.36 mol), sulfuric acid (240 mL, 4.5 mol), and deionized water (180 mL), previously prepared and cooled to 0 °C, was added dropwise at such a rate to maintain a reaction temperature of ≤15 °C. [**NOTE**! The combination of sulfuric acid, water, and isopropyl alcohol was highly exothermic and required external cooling. The sulfuric acid was first dissolved in water and then followed by the slow addition of isopropyl alcohol while the temperature was maintained at ≤5 °C.] The reaction mixture was aged with stirring at 10–15 °C for 1 h, after which the mixture was slowly diluted with deionized water (6.0 L) at 15–20 °C in a stirred vessel. The mixture was stirred for 10 min, and the layers were allowed to settle. The *lower* aqueous layer was removed and back-extracted once with methylene chloride (300 mL). [**NOTE**! The initial methylene chloride/product layer was less dense than the aqueous layer which contained the remaining sulfuric acid and generated sodium sulfate. The methylene chloride back extraction however contained relatively little product and was more dense than the aqueous layer.] The methylene chloride extracts were combined and washed twice with deionized water (2 × 150 mL) containing sodium bicarbonate (3.0 g each wash, 0.02 g/mL, 0.071 mol) and sodium sulfate (15 g each wash, 0.1 g/mL, 0.21 mol). The isopropyl nitrite/methylene chloride mixture was dried over sodium sulfate (200 g), filtered, and stored under nitrogen at 0–5 °C. The yield was 685 g (84.0%, 40–50 mol % in methylene chloride) as determined by ^{1}H NMR spectroscopy and specific gravity. This solution was used as is for the following diazotization reaction. A more concentrated product, however, could be obtained via atmospheric fractional distillation, but due to the inherent potential instability of isopropyl nitrite we chose to work with a solution.

***tert*-Butyl 1,1-Dioxo-7-diazocephalosporanate (7).** A 2-L three-necked round-bottomed flask equipped with a mechanical agitator and nitrogen bubbler was charged with *tert*-butyl 7-amino-1,1-dioxocephalosporanate (75.0 g, 0.208 mol) in ethyl acetate (750 mL). Isopropyl nitrite (24.1 assay g, 0.271 mol, 25–50 wt % in methylene chloride) was added to the stirred solution at 15–20 °C followed by a catalytic amount of trifluoroacetic acid (0.1 mL, 0.005 mol). The batch temperature rose to 31 °C over 15 min and was monitored by HPLC for completeness.

The reaction normally completed within 1 h as judged by HPLC. HPLC conditions: column, C-8 Altex Ultrasphere 5 μm (4.1 mm × 25 cm); eluant, 60:40 A:B isocratic at 2.0 mL/min, A=H_2O (0.1% H_3PO_4 v/v), B=CH_3CN; temperature, 50 °C; detector, UV at 260 nm; t_R sulfone **4**, 4.6 min; t_R diazo compound **7**, 8.3 min.

When diazotization was complete the batch was diluted with ethyl acetate (750 mL) and concentrated in vacuo at ≤30 °C to 750 mL.

[**NOTE**! In isolated form the diazo compound may be explosive; however, preliminary evaluation by our Occupational Hazards Evaluation Laboratory suggested that this material may be handled safely as a dilute solution in ethyl acetate. Therefore, it was important that product did not crystallize near the neck of the flask during concentration. The above flush/concentration removed most of the excess unreacted isopropyl nitrite, isopropyl alcohol byproduct, and methylene chloride.] The batch was then

filtered, *only if necessary*, to remove insolubles (a slight haze was permissable) and subsequently diluted to exactly 1.0 L with fresh ethyl acetate (approximately 250 mL). The mixture was then transferred to a jacketed and externally cooled 2-L reaction kettle equipped with an overhead mechanical stirrer, vacuum/nitrogen-purger control, and bottom outlet valve. The stirred batch was cooled to −5 °C, vacuum purged three times with nitrogen, and used immediately in the next step.

A small quantity of diazo compound **7** was isolated for characterization. Concentration of the ethyl acetate product solution and crystallization from ethyl acetate/hexanes afforded a yellow crystalline solid, mp 111–112 °C dec, identified as **7** based on its spectral properties. ^{1}H NMR ($CDCl_3$): δ 5.62 (d, 1 H, J = 1.2), 5.08 (d, 1 H, J = 13.5), 4.68 (d, 1 H, J = 13.5), 4.03 (dd, 1 H, J = 18.1, J = 1.2), 3.80 (d, 1 H, J = 18.1), 2.09 (s, 3 H), 1.55 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 170.5 (s), 159.6 (s), 156.6 (s), 128.8 (s), 118.9 (s), 84.9 (s), 68.6 (s), 62.2 (s), 57.5 (s), 49.9 (s), 27.8 (s), 20.7 (s). FTIR (cm^{-1}) 2101, 1760, 1709, 1645, 1346, 1318. Anal. Calcd for $C_{14}H_{17}N_3O_7S$: C, 45.28; H, 4.61; N, 11.32; S, 8.63. Found: C, 45.25; H, 4.60; N, 10.77; S, 8.43.

***tert*-Butyl 1,1-Dioxo-*trans*-7-methoxycephalosporanate (8).** Simultaneous to preparation of the diazoacephalosporanate **7** above, rhodium octanoate dimer (1.5 g, 385 mmol) was dissolved in methanol (128 mL) and diluted to exactly 1 L with ethyl acetate (approximately 850 mL). The mixture was transferred to a jacketed and externally cooled 2-L reaction kettle equipped with an overhead mechanical agitator, vacuum/nitrogen-purger control, and bottom outlet valve. The stirred mixture was cooled to −5 °C and vacuum purged three times with nitrogen. Prior to reaction with the diazocephalosporanate, triethylamine (3 mL) was added to the catalyst mixture, and the solution was stirred for 5 min. A color change from blue-green to purple occurred likely due to ligand exchange and/or complexation of the rhodium octanoate dimer with triethylamine.

The solutions of catalyst and diazocephalosporanate were then metered together (pumped) at a rate of 175 mL/min from the bottom valves of the reaction kettles through a (0.5 cm × 40 cm) Kenics static flow reactor (1/4-40-174-0) which exited into a stirred *open* 4-L flask. [**NOTE**! The above reaction rapidly eliminated 4.7 L of nitrogen gas, and could not be run in a closed vessel. Flow meters calibrated to the above solvents were useful to maintain equal mixing (±5%). A temperature rise of approximately 8 °C was observed at the mixing head.] The batch was then stirred for 5 min to allow any remaining diazo compound to react and was then neutralized with acetic acid (10 mL, 0.175 mol). Assay by HPLC against an external standard showed 66.4 g (85.0 wt %) of **8**. HPLC conditions: column, C-8 Altex Ultrasphere 5 μm (4.1 mm × 25 cm); eluant, 60:40 A:B isocratic at 2.0 mL/min, A=H_2O (0.1% H_3PO_4 v/v), B=CH_3CN; temperature, 50 °C; detector, UV at 260 nm; t_R *cis*-methoxy product **9**, 6.5 min; t_R diazo compound **7**, 8.3 min; t_R *trans*-methoxy product **8**, 9.9 min. The reaction mixture was concentrated to an oil, taken up in ethyl acetate (500 mL), washed with water (2 × 200 mL), and dried over sodium sulfate (200 g). The mixture was further concentrated to a thick oil and chromatographed over silica gel (750 g, 5:1 hexanes/ethyl acetate). The first and major product fraction contained 66 g (84 wt %) of a white crystalline solid, mp 130–130.5 °C (EtOAc/hexanes), and was identified as *tert*-butyl 1,1-dioxo-*trans*-7-methoxycephalosporanate (**8**) on the basis of its spectral characteristics. ^{1}H NMR ($CDCl_3$): δ 5.18 (d, 1 H, J = 1.4), 5.04 (d, 1 H, J = 13.2), 4.70 (d, 1 H, J = 1.4), 4.68 (d, 1 H, J = 13.2), 3.99 (d, 1 H, J = 18.4), 3.69 (d, 1 H, J = 18.4), 3.57 (s, 3 H), 2.10 (s, 3 H), 1.56 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 170.4 (s), 160.2 (s), 158.9 (s), 127.8 (s), 120.3 (s), 85.07 (s), 85.02 (s), 69.1 (s), 61.8 (s), 58.7 (s), 51.5 (s), 27.7 (s), 20.7 (s). Anal. Calcd for $C_{15}H_{21}NO_8S$: C, 48.00; H, 5.64; N, 3.73; S, 8.54. Found: C, 47.94; H, 5.76; N, 3.78; S, 8.69. The second major product fraction contained 1.1 g (4.2 wt %) of a white crystalline solid, mp 159.5–160 °C, which was identified as *tert*-butyl 1,1-dioxo-*cis*-7-methoxycephalosporanate (**9**) on the basis of its spectral characteristics. ^{1}H NMR ($CDCl_3$): δ 5.12 (d, 1 H, J = 4.4), 5.10 (d, 1 H, J = 13.9), 4.82 (d, 1 H, J = 4.4), 4.74 (d, 1 H, J = 13.9), 3.96 (d, 1 H, J = 18.4), 3.70 (d, 1 H, J = 18.4), 3.67 (s, 3 H), 2.10 (s, 3 H), 1.54 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ 170.3 (s), 162.4 (s), 159.1 (s), 125.9 (s), 123.4 (s), 85.9 (s), 84.7 (s), 67.7 (s), 62.1 (s), 60.4 (s), 51.8 (s), 27.7 (s), 20.6 (s). Anal. Calcd for $C_{15}H_{21}NO_8S$: C, 48.00; H, 5.64; N, 3.73; S, 8.54. Found: C, 48.05; H, 5.69; N, 3.67; S, 8.62.

Alternatively, the batch was then concentrated in vacuo to approximately 1.0 L, first washed with deionized water (600 mL) containing NaCl (60 g) and H_3PO_4 (85% 1.7 mL), and secondly with a solution of 10% sodium chloride (300 mL). The ethyl acetate layer was dried over Na_2SO_4 (200 g) and then passed through a bed of silica gel (0.5 kg). The silica gel was then washed with ethyl acetate (3 L) until >99% of the product had been recovered as determined by HPLC assay. The batch and wash were combined and concentrated in vacuo at <30 °C to 400 mL. Hexanes (400 mL) was slowly added, during which crystallization occurred. The crystallization mixture was further concentrated to 200 mL, diluted with hexanes (1.2 L) over 4 h, aged with stirring for 4 h at 25 °C, and then for 24 h at 0–5 °C. The batch was filtered, and the cake washed with 300 mL of hexanes. The cake was sucked well and dried in vacuo, ≤40 °C. The yield of *tert*-butyl 1,1-dioxo-*trans*-7-methoxycephalosporanate (**8**) was 60.1 g (77.0% corrected for 90 wt % purity by HPLC). The bulk of impurities was comprised of *cis*-methoxy insertion adduct **9** (5–7%).

Reaction of 7 with Hydrochloric Acid. To a cooled (−5 °C) solution of the diazo compound **7** in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a solution of HCl in ethyl acetate (31 mL, 1.38 M, 42.8 mmol). The mixture was stirred for 5 min and then washed consecutively with 5% sodium bicarbonate (20 mL), 1% aqueous H_3PO_4 (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluant. The first component isolated contained 420 mg (42%) of a crystalline solid, mp 150–151 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-chlorocephalosporanate on the basis of its spectral properties. ^{1}H NMR ($CDCl_3$): δ 5.31 (d, 1 H, J = 1.5), 5.11 (d, 1 H, J = 13.8), 4.81 (d, 1 H, J = 1.5), 4.71 (d, 1 H, J = 13.8), 4.04 (d, 1 H, J = 18.4), 3.77 (d, 1 H, J = 18.4), 2.10 (s, 3 H), 1.57 (s, 9 H). Anal. Calcd for $C_{14}H_{18}NO_7SCl$: C, 44.27; H, 4.78; N, 3.69; S, 8.44. Found: C, 44.26; H, 4.75; N, 3.64; S, 8.32.

The second component isolated contained 20 mg (2.0%) of a crystalline solid, mp 140.0 °C (EtOAC/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-chlorocephalosporanate on the basis of its spectral characteristics. ^{1}H NMR ($CDCl_3$): δ 5.35 (d, 1 H, J = 4.95), 5.16 (d, 1 H, J = 14.1), 4.92 (d, 1 H, J = 4.7), 4.74 (d, 1 H, J = 14.1), 3.98 (d, 1 H, J = 18.2), 3.70 (d, 1 H, J = 18.2), 2.10 (s, 3 H), 1.55 (s, 9 H). Anal. Calcd for $C_{14}H_{18}NO_7SCl$: C, 44.27; H, 4.78; N, 3.69. Found: C, 43.92; H, 4.58; N, 3.34.

Reaction of 7 with Hydrofluoric Acid. To a cooled (−78 °C) solution of the diazo compound **7** in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a 70% solution of HF in pyridine (0.1 mL, 3.58 mmol). The mixture was stirred for 24 h and consecutively washed with 10% sodium bicarbonate (20 mL), 1% aqueous H_3PO_4 (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluant. The first component isolated contained 54 mg (5.2%) of a crystalline solid, mp 144–145 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-fluorocephalosporanate on the basis of its spectral characteristics. ^{1}H NMR ($CDCl_3$): δ 5.94 (dd, 1 H, J_{HF} = 51.5, J_{HH} = 1.2), 5.07 (d, 1 H, J = 13.8), 4.91 (dd, 1 H, J_{HF} = 7.2, J_{HH} = 1.2), 4.69 (d, 1 H, J = 13.8), 4.04 (d, 1 H, J = 18.3), 3.73 (d, 1 H, J = 18.3), 2.11 (s, 3 H), 1.57 (s, 9 H). Anal. Calcd for $C_{14}H_{18}NO_7SF$: C, 46.28; H, 4.99; N, 3.86; S, 8.82. Found: C, 46.10; H, 4.97; N, 3.81; S, 8.63.

The second slower eluting component contained 50 mg (5.2%) of a crystalline solid, mp 136.0–138.0 °C dec, identified as *tert*-butyl 1,1-dioxo-*trans*-7-hydroxycephalosporanate on the basis of its spectral properties. ^{1}H NMR ($CDCl_3$): δ 6.39 (d, 1 H, J = 8.3), 5.40 (dd, 1 H, J = 8.3, J = 1.6), 5.10 (dd, 1 H, J = 1.6, J = 0.8), 5.06 (d, 1 H, J = 13.0), 4.68 (d, 1 H, J = 13.0), 4.29 (dd, 1 H, J = 18.2, J = 0.80), 3.95 (d, 1 H, J = 18.2), 2.05 (s, 3 H), 1.55 (s, 9 H). Anal. Calcd for $C_{14}H_{19}NO_8S$: C, 46.53; H, 5.30; N, 3.88; S, 8.87. Found: C, 46.51; H, 5.31; N, 3.83; S, 9.07.

Reaction of 7 with Ethanol. To a cooled (−5 °C) solution of the diazo compound **7** in ethyl acetate (13.2 mL containing 2.75

mmol) was added with rapid stirring a nitrogen-purged solution of rhodium octanoate dimer (20 mg), triethylamine (40 μL), and ethanol (2.5 mL, 0.0428 mol) in ethyl acetate (10 mL). The mixture was stirred for 20 min and consecutively washed with 1% aqueous H_3PO_4 (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluent. The first component isolated contained to 880 mg (86%) of a crystalline solid, mp 85.0 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-ethoxycephalosporanate on the basis of its spectral properties. ^1H NMR ($CDCl_3$): δ 5.21 (d, 1 H, J = 1.7), 5.01 (d, 1 H, J = 13.6), 4.70 (dd, 1 H, J = 1.7, J = 1.0), 4.67 (d, 1 H, J = 13.6), 3.99 (dd, 1 H, J = 18.0, J = 1.0), 3.67–3.87 (m, 2 H, CH_2), 3.69 (d, 1 H, J = 18.0), 2.10 (s, 3 H), 1.56 (s, 9 H), 1.3 (t, 3 H). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60; S, 8.23. Found: C, 49.28; H, 5.97; N, 3.55; S, 8.09.

The second component isolated contained 110 mg (11%) of a crystalline solid, mp 155.5–156.0 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-ethoxycephalosporanate. ^1H NMR ($CDCl_3$): δ 5.16 (d, 1 H, J = 4.4), 5.15 (d, 1 H, J = 13.9), 4.77 (d, 1 H, J = 4.4), 4.74 (d, 1 H, J = 13.9), 3.92 (d, 1 H, J = 18.5), 3.76–3.94 (m, 2 H, CH_2), 3.66 (d, 1 H, J = 18.5), 2.1 (s, 3 H), 1.54 (s, 9 H), 1.33 (t, 3 H, J = 7.0). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60; S, 8.23. Found: C, 49.44; H, 6.00; N, 3.56; S, 8.20.

Reaction of 7 with 2-Propanol. To a cooled (−5 °C) solution of the diazo compound 7 in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a nitrogen-purged solution of rhodium octanoate dimer (20 mg), triethylamine (40 μL) and 2-propanol (3.3 mL, 42.8 mmol) in ethyl acetate (10 mL). The mixture was stirred for 20 min and washed consecutively with 1% aqueous H_3PO_4 (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluant. The first component isolated contained 571 mg (54%) of a crystalline solid, mp 118.5–119.0 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-(isopropyloxy)cephalosporanate on the basis of its spectral characteristics. ^1H NMR ($CDCl_3$): δ 5.22 (d, 1 H, J = 1.4), 5.00 (d, 1 H, J = 13.5), 4.67 (d, 1 H, J = 13.5), 4.65 (br d, 1 H, J = 1.4), 3.99 (br d, 1 H, J = 18.2), 3.90 (septet, 1 H, J = 6.0), 3.67 (d, 1 H, J = 18.2), 2.10 (s, 3 H), 1.56 (s, 9 H), 1.29 (d, 3 H, J = 6.0), 1.26 (d, 3 H, J = 6.0). Anal. Calcd for $C_{17}H_{25}NO_8S$: C, 50.61; H, 6.25; N, 3.47; S, 7.95. Found: C, 50.51; H, 6.30; N, 3.42; S, 7.88.

The second component isolated contained 53 mg (5%) of a crystalline solid, mp 149–150 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-(isopropyloxy)cephalosporanate. ^1H NMR ($CDCl_3$): δ 5.20 (d, 1 H, J = 4.7), 5.11 (d, 1 H, J = 14.0), 4.76 (dd, 1 H, J = 4.7, J = 1.1), 4.73 (d, 1 H, J = 14.0), 3.93 (septet, 1 H, J = 6.1), 3.90 (dd, 1 H, J = 18.5, J = 1.1), 3.64 (d, 1 H, J = 18.5), 2.09 (s, 3 H), 1.54 (s, 9 H), 1.30 (d, 6 H, J = 6.1). Anal. Calcd for $C_{17}H_{25}NO_8S$: C, 50.61; H, 6.25; N, 3.47; S, 7.95. Found: C, 50.78; H, 6.26; N, 3.41; S, 7.89.

Reaction of 7 with Triethylborane. The following reaction was patterned after the procedure of Weiring and Wynberg.[16] To a cooled (−78 °C) solution of the diazo compound 7 in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a triethylborane/tetrahydrofuran solution (5.5 mL, 1.0 M, 5.5 mmol). The reaction mixture was allowed to warm to 0 °C, and the reaction was quenched with the addition of 30% H_2O_2 (0.5 mL). The mixture was washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (6/1) as the eluant. The first eluted component contained 456 mg (46%) of a crystalline solid, mp 109–110 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-ethylcephalosporanate on the basis of its spectral characteristics. ^1H NMR ($CDCl_3$): δ 5.05 (d, 1 H, J = 13.5), 4.66 (d, 1 H, J = 13.5), 4.51 (br d, 1 H, J = 1.4), 3.95 (d, 1 H, J = 18.6), 3.85 (dt, 1 H, J = 1.4, J = 7.4), 3.70 (d, 1 H, J = 18.6), 2.08 (s, 3 H), 1.92 (p, 2 H, J = 7.4), 1.54 (s, 9 H), 1.09 (t, 3 H, J = 7.4). Anal. Calcd for $C_{16}H_{23}NO_7S$: C, 51.46; H, 6.21; N, 3.75; S, 8.59. Found: C, 51.29; H, 6.25; N, 3.73; S, 8.56.

The second eluted component contained 454 mg (45%) of a crystalline solid, mp 117.5–118.0 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-ethylcephalosporanate on the basis of its spectral properties. ^1H NMR ($CDCl_3$): δ 5.05 (d, 1 H, J = 13.5), 4.73 (dd, 1 H, J = 5.3, J = 1.0), 4.66 (d, 1 H, J = 13.50), 3.93 (dd, 1 H, J = 18.3, J = 1.0), 3.78 (dt, 1 H, J = 5.3, J = 7.9), 3.61 (d, 1 H, J = 18.3), 2.16 (p, 2 H, J = 7.9), 2.09 (s, 3 H), 1.54 (s, 9 H), 1.14 (t, 3 H, J = 7.4). Anal. Calcd for $C_{16}H_{23}NO_7S$: C, 51.46; H, 6.21; N, 3.75; S, 8.59. Found: C, 51.37; H, 6.26; N, 3.70; S, 8.70.

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An Efficient Synthesis of Novel α-Diketone and α-Keto Ester Derivatives of N-Protected Amino Acids and Peptides

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A novel synthetic approach to α-diketone and α-keto ester derivatives of N-protected amino acids and peptides via a common intermediate is described. Conversion of the carboxyl group of N-protected amino acids and peptides into an α-keto vinyl ether functionality and subsequent hydrolysis or ozonolysis produces α-diketone or α-keto ester functionalities, respectively. Preparation of the α-keto vinyl ether intermediates was achieved by conversion of the protected amino acids and peptides to the corresponding *N*-methoxy-*N*-methylamides and alkylation with (α-ethoxyvinyl)magnesium bromide.

Peptidyl α-keto esters are receiving considerable attention due to their potent inhibition of various proteolytic enzymes.[1-6] Recently, we found that peptidyl α-diketones are also potent inhibitors of cysteine and serine proteinases.[6] By analogy to the mechanism established for the inhibition of serine-dependent proteases by peptidyl tri-

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